



VERDICT & SUMMARY

Levetiracetam

(Keppra®)

For the treatment of partial onset epileptic seizures

Committee's Verdict: **CATEGORY B (Q1)**

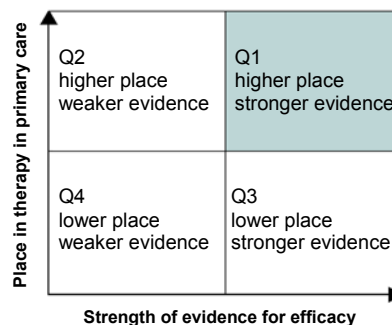
BNF: 4.8.1

Initiation and stabilisation of treatment with levetiracetam should be the responsibility of the specialist. It is then appropriate for GPs to prescribe levetiracetam for maintenance with the guidance of a shared care agreement. Patients with epilepsy are expected to receive continuing follow-up in secondary care.

Category B: suitable for restricted prescribing under defined conditions

Q1 rating: The evidence for the efficacy of levetiracetam for the treatment of partial-onset seizures was relatively strong. A large comparative RCT found that levetiracetam monotherapy was not inferior to carbamazepine. As adjunctive therapy in adults and children over four years, levetiracetam was more effective than placebo in four RCTs. As a well-established second-line antiepileptic drug, levetiracetam has a relatively high place in therapy.

The Q rating relates to the drug's position on the effectiveness indicator grid. The strength of the evidence is determined by the quality and quantity of studies that show significant efficacy of the drug compared with placebo or alternative therapy. Its place in therapy in primary care takes into account safety and practical aspects of using the drug in primary care, alternative options, relevant NICE guidance, and the need for secondary care input.



MTRAC updated the review on this drug to include extensions to the licensed indications

Licensed indications

Levetiracetam is indicated as monotherapy in the treatment of partial-onset seizures with or without secondary generalisation in patients aged 16 or over with newly diagnosed epilepsy.

Levetiracetam is indicated as adjunctive therapy in:¹

- the treatment of partial onset seizures with or without secondary generalisation in patients aged four or over with epilepsy
- the treatment of myoclonic and primary generalised tonic-clonic seizures in patients aged at least 12 with juvenile myoclonic epilepsy or idiopathic generalised epilepsy (see verdict sheet VS07/09).

Background information

Epilepsy is a serious neurological disorder characterised by recurrent, spontaneous seizures. Seizures are classified into two main groups, generalised and partial seizures, according to the area of the brain in which the abnormal discharge originates. If discharge starts in a localised area of the brain, this is called a partial seizure. Generalised seizures occur following simultaneous activation of both sides of the brain with loss of consciousness from the outset, e.g. tonic-clonic and absence seizures.²

Most patients will respond to the established antiepileptics, e.g. sodium valproate, phenytoin or

carbamazepine, but around 30% often require treatment with more than one antiepileptic drug (AED) and may continue to have seizures despite drug treatment.³ Several newer AEDs are available as monotherapy or add-on therapy in patients with refractory epilepsy, e.g. gabapentin, lamotrigine, topiramate, levetiracetam, tiagabine and zonisamide.

Levetiracetam is a pyrrolidone derivative chemically unrelated to other AEDs. The mechanism of action of levetiracetam is not known but it does not appear to involve inhibitory or excitatory neurotransmission.

Clinical efficacy

Adjunctive therapy for uncontrolled partial-onset seizures

Levetiracetam (1,000 mg to 3,000 mg/day) was evaluated as adjunctive therapy to existing AED treatment in adults over 16 years with uncontrolled partial seizures in three placebo-controlled, double-blind RCTs (n = 904; duration 8 to 16 weeks).⁴⁻⁶

Results showed that levetiracetam significantly reduced weekly partial seizure frequency compared with placebo and baseline ($p \leq 0.006$).⁴⁻⁶ The 50% responder rate (number of patients showing 50% or greater reduction in seizure frequency) was significantly higher for all evaluated doses of levetiracetam compared with placebo ($p \leq 0.019$). The number of seizure-free patients was significantly higher for the levetiracetam 3,000 mg daily dose than

placebo ($p \leq 0.019$).

Monotherapy for partial-onset seizures

In a large comparative RCT ($n = 579$; duration 26 weeks),⁷ levetiracetam (1,000 mg to 3,000 mg) was compared with carbamazepine (400 mg to 1,200 mg) as monotherapy in patients with newly diagnosed epilepsy. Results for the primary outcome, which was the percentage of patients who were seizure free for six months on the last evaluated dose, showed that 67% of patients in both levetiracetam and carbamazepine groups were seizure free (treatment difference 0.1%, 95% CI -7.4% to 7.5%).⁷

Levetiracetam was shown in this trial to be non-inferior to carbamazepine.

In one of the RCTs described above,⁶ patients who showed a response to adjunctive levetiracetam treatment were entered into a 12-week monotherapy phase. Twenty percent of levetiracetam-treated patients and 9.5% of placebo-treated patients completed this phase ($p = 0.029$ vs. placebo).⁶

Adjunctive therapy for uncontrolled partial-onset seizures in children

A double-blind, placebo-controlled RCT ($n = 216$; 14 weeks)⁸ evaluated levetiracetam 20 to 60 mg/kg/day as adjunctive treatment to existing AEDs in children aged 4 to 16 years. Levetiracetam-treated patients showed a significantly greater median percentage reduction in weekly partial seizure frequency than placebo (43% vs. 16%, $p < 0.0001$) and significantly more levetiracetam-treated patients responded to treatment (45% vs. 20% of placebo patients, $p < 0.0001$).⁸ Seven levetiracetam-treated patients (7%) were seizure free during treatment compared with one placebo-treated patient (1%).⁸

Adverse effects

Adverse events observed more frequently with levetiracetam 1,000 mg to 4,000 mg/day were somnolence, asthenia, headache, infection and dizziness. In a safety and tolerability study, the incidence of somnolence was greatest in the highest levetiracetam dosage group (2,000 mg bd).⁹ Asthenia was most commonly reported in patients in the lower dosage group (1,000 mg bd). See the Summary of Product Characteristics (SPC) for further details.¹

NICE guidance

In March and April 2004, the National Institute for Health and Clinical Excellence (NICE) recommended the use of monotherapy with older AEDs as first line treatment for epilepsy.^{10,11} The newer AEDs should be used, within their licensed indications, in patients who have not benefited from treatment with older AEDs or for whom older drugs are contraindicated.

NICE emphasized the importance of appropriate follow-up arrangements and the use of shared care arrangements where necessary for all patients.

Additional information

Three different levetiracetam formulations are available: tablets, oral solution and solution for infusion.

As monotherapy, the recommended starting dose is 250 mg twice daily, increased to 500 mg twice daily after two weeks. For adjunctive therapy the recommended initial dose of levetiracetam is 500mg twice daily. In all patients the dose can be increased depending on clinical response and tolerance to a maximum of 1,500 mg twice daily.¹ Refer to the SPC for full guidance.¹

At current prices, one year's treatment with levetiracetam tablets 1,000 to 3,000 mg/day costs £636 to £2,168.

References

1. UCB Pharma Ltd. Keppra. *Summary of Product Characteristics* 2007.
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3. LaRoche SM, Helmers SL. The new antiepileptic drugs. *JAMA* 2004;**291**:605-614.
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8. Glauser TA, Ayala R, Elterman RD *et al.* Double-blind placebo-controlled trial of adjunctive levetiracetam in pediatric partial seizures. *Neurology* 2006;**66**:1654-1660.
9. Betts T, Waegemans T, Crawford P. A multicentre, double-blind, randomized, parallel group study to evaluate the tolerability and efficacy of two oral doses of levetiracetam, 2000 mg daily and 4000 mg daily, without titration in patients with refractory epilepsy. *Seizure* 2000;**9**:80-87.
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11. Newer drugs for epilepsy in children. National Institute for Health and Clinical Excellence. April 2004. <http://www.nice.org.uk/guidance/TA79/guidance/pdf/English>

Launch date: November 2000

Manufacturer: UCB Pharma Ltd

EU/1/00/146/004,10,17,24,27,30

WARNING: This sheet should be read in conjunction with the Summary of Product Characteristics
This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.

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(THIS VERDICT AND SUMMARY SHEET REPLACES VS05/09)

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VS07/08



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